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Date March 15, 1999

To Examiner Gary Kunz
U.S. Patent and Trademark Office
Art Group: 1623
Washington, DC 20231

Facsimile number 08269 00300001 (703) 308-4556

From Kathleen J. Philpot
Secretary to Janis K. Fraser, Ph.D., J.D.

Re U.S. Patent Application No. 08/849,686
Attorney Docket No. 08269/003001
Courtsey Copy of Response to Examiner's Action
dated August 17, 1998

Number of pages including this page 15

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ATTORNEY DOCKET NO. 08269/003001 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Arne Helge Deggerdal et al.
Serial No.: 08/849,686
Filed : August 21, 1997
Title : ISOLATION OF NUCLEIC ACID

Art Unit: 1623
Examiner: Gary Kunz

OFFICIAL

Assistant Commissioner for Patents
Washington, DC 20231

RESPONSE TO OFFICE ACTION DATED AUGUST 17, 1998

REMARKS

Reconsideration of the application is respectfully requested in view of the following remarks.

The Invention

The present invention includes a solid-phase method for nucleic acid isolation without using chaotropes, which are reagents that denature proteins. In this method, nucleic acids bind to a solid support made of an organic (i.e, carbon-based) polymer such as latex, polyurethane, or polystyrene, in the presence of a detergent and the absence of any chaotrope. A kit for practicing the method is also included within the scope of the invention.

Pending Claims

Claims 1-24 are pending and have been rejected on various grounds, discussed below.

Date of Deposit DECEMBER 16, 1998
I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Kathleen Shilpot
KATHLEEN SHILPOT

Rejection under 35 U.S.C. § 112, first paragraph (best mode)

Claims 1-24 are rejected for alleged concealment of the best mode contemplated by the inventors. Applicants respectfully traverse this rejection.

The Office Action refers to the following factual bases as evidence of concealment of the best mode:

> 1) applicant's working examples employs exclusively DNA/Dynabeads DNA Direct™; 2) applicant has not specifically taught how to prepare the superparamagnetic polystyrene beads called DNA/Dynabeads DNA Direct™; and 3) applicant has not specifically disclosed the composition of the "Washing Buffer" on page 4, line 1 of the product instructions.

Applicants respectfully point out that these factual bases are not accurate nor should they be used as evidence for concealment of the best mode.

First, applicants' working examples employ types of Dynabeads® other than Dynabeads DNA Direct™. For instance, Examples 1, 2, 3, and 5 refer to the use of Dynabeads® M-280*, which are "obtainable by autoclaving a suspension of Dynabeads® M-280 tosylactivated" (page 19, lines 7-8); and Example 4 refers to the use of Dynabeads® M-450 uncoated (page 21, line 29). Therefore, the Dynabeads® products exemplified in the present specification represent different kinds of Dynabeads® and are not limited "exclusively" to Dynabeads DNA Direct™ as stated by the Examiner.

Second, the specification fully enables the preferred superparamagnetic particles disclosed. The specification states that Dynabeads® are especially preferred for the present

invention, *i.e.*, "[t]he well-known magnetic particles sold by Dynal AS (Oslo, Norway) as DYNABEADS, are particularly suited to use in the present invention." (page 10, lines 36-37 and page 11, lines 1-2). Both Dynabeads® M-450 and Dynabeads® M-280 were publically available at the time the priority application was filed, *i.e.*, December 12, 1994. Evidence of the availability of these Dynabeads is provided by the attached copy of Dynal's 1989 Product List (Exhibit A). Furthermore, other superparamagnetic particles (sold by Promega Corporation) were also available at the priority date, and have been shown to be suitable for use in the claimed methods. See the copy of Promega's 1991 Protocols and Application Guide for Streptavidin paramagnetic particles attached as Exhibit B.

The Office Action asserts that the best mode is not enabled because "applicant has not specifically taught how to prepare the superparamagnetic polystyrene beads called DNA/Dynabeads DNA Direct™." This assertion premises on the Examiner's assumption that all working examples use exclusively Dynabeads DNA Direct™. In view of the above discussion, such assumption is unfounded. Dynabeads DNA Direct® is not the exclusively exemplified and preferred embodiment, as characterized by the Office Action, given that other Dynabeads® products sold by Dynal AS are specifically taught in the specification as preferred embodiments. Therefore, whether the best mode of the present invention is enabled does not depend on whether Dynabeads DNA Direct® is enabled.

That said, Applicants submit that Dynabeads DNA Direct® is in fact fully enabled. The specification teaches how to make both superparamagnetic particles and the coatings thereof. See page 10, lines 32-36 and page 11, lines 3-12 in the specification. These particles can be readily used to produce particles equivalent to Dynabeads DNA Direct™. The specification also teaches that the Dynabeads DNA Direct™ Kit contains beads equivalent to Dynabeads® M-280*, which as discussed above were taught in the specification as being generated from beads which were publically available at the time the priority application was filed. See page 23, lines 1-4 in the specification. Therefore, the Dynabeads® included in Dynabeads DNA Direct™ were enabled and readily available to one skilled in the art at the time the priority application was filed.

Third, contrary to the Office Action's assertion that "Washing Buffer" is part of the best mode, the "Washing Buffer" is merely a regular buffer used in an optional "washing step" for the purpose of convenience. This is evidenced from the specification teaching:

> Although not necessary, it may be convenient to introduce one or more washing steps to the isolation method of the invention, for example following separation of the support from the sample. In the case of magnetic beads, this may conveniently be done before releasing the DNA from the beads. Any conventional washing buffers or other media may be used. Generally speaking, low to moderate ionic strength buffers are preferred, e.g., 10 mM Tris-HCl at pH 8.0/10mM NaCl. Other standard washing media, e.g., containing alcohols, may also be used, if desired. (page 11, lines 36-37 and page 12, lines 1-9 in the specification).

Therefore, use of a washing buffer was not contemplated by the applicants as essential or critical for the present invention. Even if it were, suitable washing buffers were fully disclosed. Thus, the kit's "Washing Buffer" is not part of the best mode.

In summary, the present invention discloses the preferred embodiments and fully teaches how to make and use such preferred embodiments. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-24 stand rejected as being allegedly not enabled. This rejection is respectfully traversed.

The Office Action objects to the breadth of the claims with respect to "any and all organic solid supports." It states

> The artisan would find it incredible that any and all organic solid supports would bind DNA and permit elution of DNA in view of applicant providing working examples using a single solid support, *i.e.*, DNA/Dynabeads DNA Direct™.

It has long been held by the Court of Appeals for the Federal Circuit and its predecessor that

> A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Brana, 34 USPQ2d 1437, 1441 (Fed. Cir. 1995) citing In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971)

According to the enablement standard set forth by the Court in In re Brana, the present invention is fully enabled.

First, the specification teaches that many different kinds of useful solid supports can be used for the present invention. See the following quotation from page 9 of the specification:

> The solid support may be any of the well known supports or matrices which are currently widely used or proposed for immobilisation, separation etc. These may take the form of particles, sheets, gels, filters, membranes, fibres, capillaries, or microtitre strips, tubes, plates or wells etc.
>
> Conveniently the support may be made of glass, silica, latex or a polymeric material.

While the present claims are limited to a solid support comprising an organic polymer, the above does serve to indicate the broad scope of materials which are taught as being useful. The specification further states, at pages 10 and 11, that many different types of surfaces have in fact been used successfully:

> Non-magnetic polymer beads suitable for use in the method of the invention are available from Dyno Particles AS (Lillestrøm, Norway) as well as from Qiagen, Pharmacia and Serotec . . . Especially preferred are superparamagnetic particles for example those described by Sintef in EP-A-106873 . . . The well-known magnetic particles sold by Dynal AS (Oslo, Norway) as DYNABEADS are particularly suited to use in the present invention . . . Weakly and strongly positively charged surfaces, weakly negatively charged neutral surfaces and hydrophobic

surfaces eg. polyurethane-coated have been shown to work well.

Second, the specification also exemplifies multiple solid supports by using different Dynabeads®. For instance, Examples 1, 2, 3, and 5-13 use Dynabeads® M-280* (page 19, lines 7-8 and page 20, line 19), while Example 4 uses Dynabeads® M-450 Uncoated (page 21, line 29). These different types of Dynabeads® utilize different surface materials, i.e., polyurethane and epoxy, and thus demonstrate that a variety of organic solid support materials can be used to practice the present invention.

Third, Applicants have tested a number of other surface materials having weakly negative to positively charged surfaces, including the following:

(1) a mixture of diidocyanate/diethyleneglycol/ tetraethyleneglycol and 1,8-diamino-3,6-dioxaoctane;

(2) a mixture of polyurethane and 1,8-diamino-3,6-dioxaoctane;

(3) a hydrolysed silane epoxy; and

(4) a mixture of polyurethane and jeffamine (PEG600 with amine).

All of these were found to absorb DNA when used in the claimed methods.

To justify the rejection, the Office Action merely states, without support, that "[t]he artisan would find it incredible that any and all organic solid supports would bind DNA and permit elution of DNA." As stated above, the PTO has the initial burden of challenging a presumptively correct assertion

of utility in the disclosure. The specification teaches that any known solid supports containing an organic polymer can be used to isolate nucleic acid from a sample. The specification discloses and exemplifies a variety of such solid supports suitable for the present invention. In the absence of any evidence showing that one of ordinary skill in the art would reasonably doubt the applicants' teaching, the specification teaching "must be taken as in compliance with the enabling requirement." *Id.* The Office Action simply states a speculation and fails to make a *prima facie* nonenablement case. Therefore, the rejection is unfounded, and its withdrawal is respectfully requested.

CONCLUSION

Applicants submit that the grounds for rejection asserted by the Examiner have been overcome, and that the claims, as now pending, define subject matter that is fully enabled. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

A Petition for Extension of Time and a check covering the extension fee are enclosed herewith.

Please charge any additional fees, or apply any credits, in this matter to Deposit Account No. 06-1050 referencing attorney docket no. 08269/003001.

Respectfully submitted,

Date: Dec. 16, 1998

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

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343511.B11

EXHIBIT A

DYNAL

Encl. 1

PRODUCT LIST 1989

DYNABEADS™ products are based on extremely uniform, superparamagnetic polystyrene beads. Consisting of a maghemite (Fe_2O_3) containing core covered with a polymer, they have a smooth surface that is easily coated with antibodies or other selecting molecules. Combined with a magnet, Dynabeads make a unique tool in positive or negative separationes.

Fields of applications include:
Immunology, Tissue Typing, Cancer research, Transplantation medicine, Microbiology, Virology, DNA Technology and Clinical chemistry.

DYNABEADS UNCOATED

	Prod.no.	Volume
A. Immunomagnetic beads *for cell separations*. Uniform, superparamagnetic polystyrene beads with diameter 4.5 micron (c.v.< 5%). $4x10^8$ DYNABEADS per ml (30 mg per ml) in aquous solution.		
DYNABEADS M-450 Uncoated For *physical* adsorption of primary antibodies of the IgM class, or for customer's own secondary antibodies. Primary monoclonal antibodies of the IgG class should be bound to Dynabeads M-450 via a secondary antibody for optimal function.	140.01 140.02	2 ml 10 ml
DYNABEADS M-450 Tosylactivated For convenient *chemical* coupling of proteins or secondary antibodies of customers own choice.	140.03 140.04	2 ml 10 ml
B. Immunomagnetic beads for use *in microbiology and immunoassays*. Uniform superparamagnetic polystyrene beads with a polymer surface having only primary OH groups and with a diameter of 2.8 micron (c.v.< 3%). 6-7x10⁸ DYNABEADS per ml (10 mg per ml) in aquous solution.		
NEW **DYNABEADS M-280 Tosylactivated** For convenient chemical coupling of proteins, peptides or secondary antibodies of customers own choice. Dynabeads M-280 are activated by use of p-toluene suphonyl chloride and ready for coating through a simple incubation.	142.03 142.04	2 ml 10 ml

EXHIBIT B

Encl. 4

Promega Protocols and Applications Guide

Second Edition

Part Number Y981

The Promega *Protocols and Applications Guide* text pages are printed on recycled paper.

Promega

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FAX 608-273-6967
Telex 620677092

CE WORLDWIDE

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Nucleic Acid Detection, Purification and Labeling

Encl. 3

Contents

(continued)

Protocols for the following protein detection and purification applications are provided elsewhere in this guide:

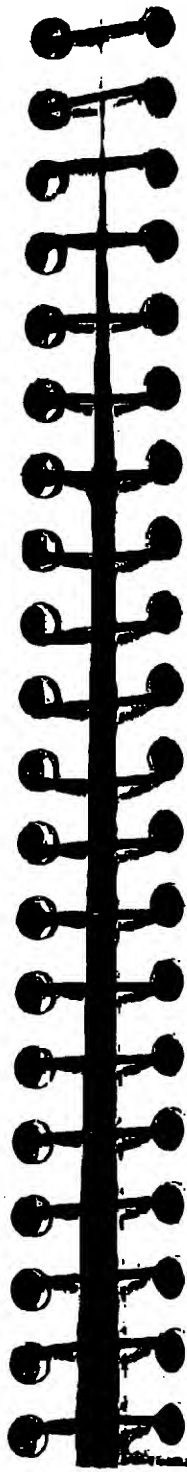
I. Magnetic Particle Separation of Macromolecules

The attachment of nucleic acids to solid supports such as nitrocellulose (1,2) and cellulose (3) has found many applications in the field of molecular biology, particularly for affinity purification of proteins and nucleic acids. One common application of immobilized nucleic acids is oligo(dT) cellulose purification of messenger RNA (mRNA) by hybridization to the 3' polyadenine tail (4). Recent years, however, have witnessed the emergence of paramagnetic particles as the solid support of choice for many affinity purification protocols. Paramagnetic particles incorporate iron oxide into submicron sized particles which have no magnetic field but form a magnetic dipole when exposed to a magnetic field. The use of paramagnetic particles eliminates the need for traditional column chromatography, centrifugation, or any other special equipment. These particles have been successfully used in the development of immunoassays (5), probe diagnostic assays (6), and for measuring RNA in cell lysates using dA-tailed capture probes (7).

Promega has extended the use of paramagnetic particles to the affinity purification of polyadenylated mRNA with the PolyATtract™ system and to cDNA synthesis and cloning with the Capture Clone™ system. Unlike procedures which use direct coupling of probes to paramagnetic particles (6,7), these systems use a biotinylated oligonucleotide probe to hybridize in solution to the targeted nucleic acid. The hybrids are then captured using covalently coupled streptavidin paramagnetic particles. This approach combines the speed and efficiency of solution hybridization with the convenience and speed (<1 minute) of magnetic separation.

Promega utilizes its own highly purified streptavidin for the production of the particles. These streptavidin paramagnetic particles (SA-PMPs) exhibit a high binding capacity for biotinylated oligonucleotides and low non-specific binding of nucleic acids. The binding capacity of the particles varies with the specific oligonucleotide probe used. For biotinylated oligo(dT), the calculated binding capacity is roughly 1nmole probe captured/mg SA-PMPs.

Promega



II. Rapid Isolation of Total RNA

A. Introduction

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PATENT
ATTORNEY DOCKET NO. 08269/003001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Arne Helge Deggerdal et al. Art Unit: 1623
Serial No.: 08/849,686 Examiner: Gary Kunz
Filed : August 21, 1997
Title : ISOLATION OF NUCLEIC ACID

Assistant Commissioner for Patents
Washington, DC 20231

PETITION FOR ONE-MONTH EXTENSION OF TIME

Pursuant to 37 C.F.R. 1.136, applicants hereby petition that the period for response to examiner's action mailed August 17, 1998, be extended for one month to and including December 17, 1998.

Enclosed is a check for $110.00 for the required fee. Please apply any other charges or any credits to our Deposit Account No. 06-1050.

Respectfully submitted,

Date: Dec. 16, 1998

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

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343511.B11

Date of Deposit December 16, 1998
I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Lisa G Gray
Lisa G Gray